Strategies for the Treatment of Antidepressant-Related Sexual Dysfunction

John Zajecka, M.D.

Sexual dysfunction and dissatisfaction are common symptoms associated with depression. Optimal antidepressant treatment should result in remission of the symptoms of the underlying illness and minimize the potential for short- and long-term adverse effects, including sexual dysfunction. Sexual dysfunction and dissatisfaction are frequently persistent or worsen with the use of some antidepressant medications; this sexual dysfunction and dissatisfaction can have negative impact on adherence to treatment, quality of life, and the possibility of relapse. Successful management of sexual complaints during antidepressant treatment should begin with a systematic approach to determine the type of sexual dysfunction, potential contributing factors, and finally management strategies that should be tailored to the individual patient. The basic physiologic mechanisms of the normal sexual phases of libido, arousal, and orgasm and how these mechanisms may be interrupted by some antidepressants provide a framework for the clinician to utilize in order to minimize sexual complaints when initiating and continuing antidepressant treatment. This article provides guidelines, based upon this type of model, for the assessment, management, and prevention of sexual side effects associated with antidepressant treatment. *(J Clin Psychiatry 2001;62[suppl 3]:35–43)*

Sexual function and satisfaction are important issues during treatment with antidepressants. Sexual problems are frequently a symptom of the underlying illness (e.g., major depression, anxiety disorders) being treated and may also be a side effect of some antidepressants. The optimal goal of treating any illness with an antidepressant should be full symptomatic recovery and minimal side effects, including preservation of sexual function and satisfaction. Failure to achieve these goals may result in several possible consequences including inadequate recovery, impaired quality of life, nonadherence to treatment, and relapse. Optimal treatment with antidepressants does not compromise sexual health but does require the clinician to assess sexual functioning at the start of and throughout treatment. Problems with sexual function and satisfaction can be assessed and managed successfully with a number of strategies.

Sexual dysfunction is a common problem reported with many antidepressants during acute and long-term treatment. The first step in the management of sexual dysfunction during antidepressant treatment is to define the actual complaint and then attempt to determine the etiology. The clinician should attempt to define which part of the normal sexual cycle is affected, namely, interest (desire), arousal, and/or orgasm. It is also important to consider whether a primary problem in one phase may be influencing another phase (e.g., inability to reach orgasm may eventually result in a decrease in desire). The clinician needs to consider all possible factors that may be impacting sexual function. Multiple factors can impact the various phases of sexual function for any individual at different times (Figure 1). Understandably, it is critical that the clinician obtain as much information regarding sexual health before starting an antidepressant in order to have baseline information, which may help define the dysfunction as well as possible causes over time. This information can then be used to find an effective strategy for solving the problem.

Prior to starting an antidepressant, the clinician should obtain information on current sexual function and satisfaction, including changes that may have occurred as a result of the patient's current illness. Inquiry about sexual health should be routine with the use of any antidepressant. Sexual function should be addressed just as a clinician addresses any other symptom of the illness for which the antidepressant is being used. Patients should be told at the initiation of treatment that, like any other symptom of their illness, difficulties with their sexual health should improve over time. Similarly, patients should be educated at the initiation of treatment about possible side effects, including sexual side effects, that may occur early or later in treatment. These strategies may make it easier for the

From the Woman's Board Depression Treatment Research Center, Rush-Presbyterian St. Luke's Medical Center, Chicago, Ill.

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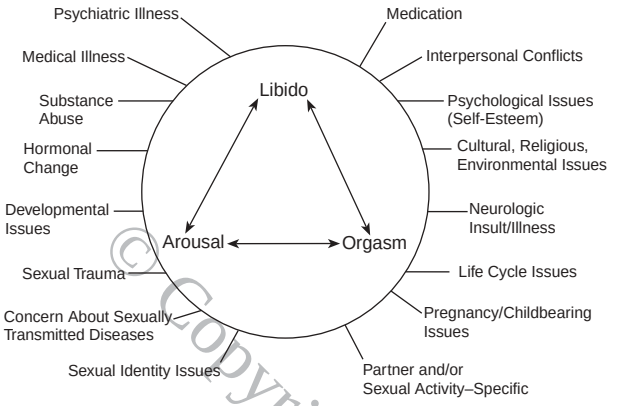
Reprint requests to: John Zajecka, M.D., 1725 W. Harrison St., Suite 955, Chicago, IL 60612.

Figure 1. Potential Causes of Sexual Dysfunction During Antidepressant Therapy



patient to discuss any sexual difficulties and should help the clinician better ascertain the cause(s) of any sexual problems, at baseline and throughout treatment.

One of the most helpful strategies in approaching sexual complaints during the course of antidepressant treatment is to determine any temporal relationship between the onset of the complaint and the symptoms of the underlying illness, treatment effects, and any other possible factors that may impact sexual function. Once the etiology of the sexual problem is determined, including factors attributed to an antidepressant, the management can be tailored to the individual needs of the patient.

THE PATHOPHYSIOLOGY OF ANTIDEPRESSANT-RELATED SEXUAL SIDE EFFECTS

Determining a strategy to manage antidepressant-related sexual side effects requires a basic understanding of the physiologic aspects of the normal sexual cycle and the impact that antidepressants may have on the interruption of these processes. The incidence of sexual side effects is high among the traditional antidepressants, such as the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and venlafaxine.[1–12] The TCAs and MAOIs commonly affect all 3 phases of the sexual cycle, namely, libido, arousal, and orgasm.[1,2,4,13–15] In comparison, the SSRIs and venlafaxine appear to have less negative impact on the first 2 phases but are commonly associated with orgasm-related dysfunction.[16–19] Data suggest that nefazodone, bupropion, and possibly mirtazapine have relatively minimal or no negative impact on any phase of the sexual cycle.[20–24] The different pharmacologic profiles of these antidepressants add to our understanding of how some antidepressants affect sexual function and provide a framework for the selection of a pharmacologic antidote, if required, for the management of the side effects.

Pathophysiology of Decreased Libido

The effect of an antidepressant on libido may be the result of multiple factors that impact areas of the central nervous system associated with sexual interest. The mesolimbic system has been shown to be associated with sexual interest, and dopamine has been implicated as one of the neurotransmitters required for maintaining sexual interest in this area.[25–28] Potent and selective serotonin reuptake blockade, associated with some antidepressants, has been implicated in reducing dopamine activity in the mesolimbic system via the serotonin-2 (5-HT_2) receptor.[28–30] This may explain why antidepressants that antagonize (block) the 5-HT_2 receptor (e.g., nefazodone), or have minimal or no effect on the serotonin reuptake system (e.g., bupropion), are not associated with reduced libido. Modulation of the 5-HT_{1A} receptor, via agonist effects, with pharmacologic agents such as buspirone demonstrates facilitation of sexual activity in animal models. The 5-HT_{1A} receptor, coupled with other serotonin receptors, may play an important role in the effect of depression, anxiety, and pharmacologic agents that may alter sexual function.[26]

Several antidepressants (e.g., SSRIs) have been associated with increasing prolactin levels, which can have secondary effects on the central nervous system, resulting in diminished libido.[31–35]

The impact of antidepressants on arousal and/or orgasm is frequently associated with diminished libido over time and should be considered in patients who initially complain of difficulties with arousal (e.g., erection or vaginal lubrication) or orgasm dysfunction. Difficulties in the later phases may have an indirect effect on libido; they may be managed by addressing the primary sexual phase disrupted by the antidepressant.

Pathophysiology of Arousal Dysfunction

Sexual arousal in males includes the ability to achieve and maintain an erection and in females includes clitoral engorgement and vaginal lubrication during sexual stimulation. Sexual arousal appears to be mediated by both central and peripheral nervous systems.[25,26] Sexual arousal is partially mediated centrally in the mesolimbic system (pleasure/reward) by dopamine and can be interrupted via potent and selective serotonin reuptake inhibition, similar to the impact on libido.[25,26] Peripherally, sympathetic and parasympathetic activity mediates the spinal reflexes associated with erection and clitoral engorgement and are mediated by serotonin and other neurotransmitters that impact sympathetic/parasympathetic tone.[25,26] Potent and selective serotonin reuptake inhibition may result in inhibition of these important peripheral spinal reflexes.[25,26,36] This may explain the high incidence of difficulties with arousal associated with the anticholinergic agents (e.g., TCAs).

Nitric oxide has recently been implicated to play a role in mediating sexual arousal at a peripheral level by mediating vascular changes required for erection.[37] Sildenafil is

a potent phosphodiesterase inhibitor that augments nitric oxide peripherally, resulting in smooth muscle relaxation and inflow of blood to the genital organs (e.g., the penis).[38] One study[37] demonstrated that the SSRI paroxetine reduced nitric oxide levels throughout the first 6 weeks of treatment, an effect that was not demonstrated with the TCA nortriptyline. The clinical relevance and extrapolation to other SSRIs are not known.

Direct effects of an antidepressant on diminishing libido and/or orgasm can have indirect effects over time on sexual arousal.

Pathophysiology of Orgasm Dysfunction

While the central nervous system may have some impact, orgasm and ejaculation appear to be primarily mediated at the peripheral spinal level. Sympathetic and parasympathetic tones are important in mediating orgasm and ejaculation and are at least partly dependent upon norepinephrine and dopamine activity, which are mediated by the 5-HT_2 receptor.[10,26,36,39] Potent and selective serotonin reuptake inhibition is thought to result in a 5-HT_2–mediated decrease of the norepinephrine and dopamine activity required for orgasm and ejaculation. This decrease may account for the high incidence of orgasm delay/anorgasmia with SSRIs relative to antidepressants that have less-potent (e.g., nefazodone, mirtazapine) or no serotonin reuptake blocking effects (e.g., bupropion) and have the additional benefit of 5-HT_2 antagonism (e.g., nefazodone, mirtazapine).

Antidepressants that have potent serotonin reuptake inhibition (e.g., SSRIs) have been associated with subjective reporting of diminished sensations in the genital areas, often referred to as "genital anesthesia."[10,11,40,41] Nociceptive sensation is partially modulated by serotonin and may partially explain orgasm delay/anorgasmia associated with diminished sexual sensations.

These models provide a framework for the clinician to consider when choosing an antidepressant for a patient, determining the association between a sexual side effect and an antidepressant, and choosing a particular management strategy (e.g., pharmacologic antidote) to "counteract" a particular sexual side effect.

GUIDELINES FOR MANAGING ANTIDEPRESSANT SEXUAL SIDE EFFECTS

Table 1 summarizes some of the general issues to consider in the management of antidepressant sexual side effects. Choosing an antidepressant with a favorable side effect profile, including consideration of sexual side effects at the initiation of treatment, would be the ideal situation. An emerging literature indicates that the newer antidepressants such as nefazodone, bupropion, and possibly mirtazapine have minimal or no negative impact on sexual functioning and are as effective as traditional agents. These antidepressants possess pharmacologic properties different from those of traditional antidepressants that make them favorable choices as first-line treatments and/or when needing to switch antidepressants because of side effects such as sexual side effects. However, sexual side effects associated with other antidepressants can often be managed successfully. There are several possible strategies to consider when sexual dysfunction/dissatisfaction is determined to be related to an antidepressant. These options include (1) reduce antidepressant to a minimal dose, (2) wait for adaptation to occur, (3) switch to another antidepressant, (4) utilize "drug holidays," or (5) use pharmacologic antidotes (see Table 1).

Table 1. General Guidelines in Managing Antidepressant-Induced Sexual Dysfunction

Choose an antidepressant at the initiation of treatment with a favorable side effect profile
Wait for adaptation to occur
Reduce to minimal effective dose
Use pharmacologic antidotes
Switch to another antidepressant
Consider "drug holiday"

Whichever strategy is used, it should always be tailored to the individual patient. It is important to consider several factors, including the efficacy of the current treatment, other side effects, comorbid illness, severity of the side effect, and compliance issues resulting from the side effect. The management of sexual side effects in patients who have a partial but good response to the current treatment may be different from management in patients who are having a full response to treatment but have numerous other side effects and are at risk of stopping the treatment on their own.

Reduce Dose of Antidepressant

Antidepressant sexual side effects appear to be dose related.[9,42–44] Gradual reduction of the dose may be useful for some patients, provided that they have achieved a full response and that the dose does not compromise efficacy.[9,42,43] Dose reduction can be particularly useful if the patient is also having other side effects. Watching for reemergence of depressive symptoms is important, especially when reducing antidepressants that have a dose-response effect. Watching for any symptoms of the antidepressant discontinuation syndrome is also important, particularly for rapid dose reduction with a short–half-life antidepressant. These symptoms may be attributed to a reemergence of the illness or to new side effects.[45]

Wait for Adaptation

Although there is a paucity of data pertaining to how long sexual side effects may last with a particular antidepressant, some patients report that sexual side effects improve over time.[9,42] Clinical practice suggests that adapta-

tion to sexual side effects occurs when the initial complaints are mild and most often when they are associated with delayed orgasm, rather than libido or arousal complaints.[9,42] This approach can be used either alone or in conjunction with other strategies such as lowering the dose or adding a pharmacologic antidote, especially if the patient and/or partner is aware that the side effect will be monitored over time. Although there are few data regarding the effect of waiting for tolerance to develop, in a series of 156 patients with SSRI-related sexual side effects,[42] only 19% reported moderate-to-complete improvement of side effects at 4 to 6 months. This series of patients supports observation in clinical practice that if the sexual side effect does not abate within 4 to 6 months, it is likely to persist unless other strategies are used.[42,46]

Switch Antidepressants

Several studies suggest that switching to an antidepressant associated with less severe sexual side effects may be an effective strategy for some patients. Studies[21,22,24] suggest that patients experiencing sexual side effects while taking an SSRI show improvement in the side effects when switched to nefazodone, bupropion, or mirtazapine. In at least 1 study,[21] patients switched from sertraline to nefazodone showed improvement in their sexual side effects without losing antidepressant effects. In another study,[22] in which patients were switched from an SSRI to bupropion, 64% of the patients experienced improvement of their sexual functioning; however, 36% dropped out of treatment, owing to a new side effect or lack of efficacy. Concerns related to switching antidepressants are evident in such studies, namely the concerns that new side effects may emerge and that some patients may relapse when switched to an antidepressant with a different pharmacologic profile. The concern about relapse is obviously most important when patients are demonstrating a full response to the initial treatment. The differences between the 2 studies mentioned above in sustaining efficacy may be explained by the fact that nefazodone and SSRIs both inhibit serotonin reuptake, with the added benefit for nefazodone of having 5-HT_2 antagonism, which probably explains its "protective" effects against sexual side effects. Bupropion has a pharmacologic mechanism hypothesized to be independent of serotonin activity, and therefore it represents a switch to a class of antidepressant with a mechanism different from that of the SSRIs, which the patients were apparently responding to before the switch. While further studies are clearly needed to further elucidate the effectiveness of switching from one antidepressant to another owing to sexual side effects, the clinician should consider switching to an antidepressant with at least a similar pharmacologic profile to the initial treatment if the initial treatment is effective. Switching antidepressants remains a reasonable first-line approach in patients who are not responding adequately to the initial treatment.

Drug Holidays

Rothschild[47] showed that stopping sertraline and paroxetine over 48 hours was an effective strategy that improved libido, orgasm dysfunction, and sexual satisfaction for at least 50% of 4 weekend "drug holidays," when these SSRIs were associated with sexual side effects. Similar improvement was not observed in patients given "drug holidays" while taking fluoxetine, which is most likely the result of the long half-life of fluoxetine. Drug holidays may be an effective strategy for patients taking short–half-life antidepressants. The clinician may choose to lower the dose in some patients rather than abruptly discontinue treatment, particularly with antidepressants associated with the potential for an acute onset of discontinuation symptoms (e.g., venlafaxine, paroxetine).[45] If using this strategy, clinicians need to inform patients of the possible emergence of antidepressant discontinuation symptoms and reinforce the importance of antidepressant compliance in order to avoid patients' skipping doses too often and risking relapse. This strategy is not recommended for patients who are known to have a history of noncompliance with their antidepressant, expect to use "drug holidays" frequently, or are not fully responding to the treatment.

PHARMACOLOGIC ANTIDOTES

There is a growing literature on the use of pharmacologic antidotes for the treatment of sexual side effects. Antidotes can be an effective strategy to manage sexual side effects in patients who are responding adequately to their treatment and in patients who are partially responding to treatment or having other side effects for which an antidote may be of additional benefit.

Very few controlled studies assess the safety and efficacy of pharmacologic antidotes, and most are case series or reports. When choosing an antidote, the clinician needs to consider what has been reported to be effective to treat a specific sexual side effect with a specific antidepressant and utilize the basic pathophysiologic framework that may explain the side effect. This is where the treatment must be tailored to the individual patient and where the clinician practices both the art and science of medicine. The clinician needs to take into account several factors when using this strategy to manage sexual side effects, including whether the antidepressant is showing efficacy to treat the underlying illness, the potential for clinical consequences of drug interactions, potential new side effects, the cost of an additional medication, and potential additive effects of enhancing efficacy or managing other side effects. Clinical experience suggests using most pharmacologic antidotes on a daily standing basis, since little is known as to how long they may take to become effective. Exceptions may include sildenafil, which has been shown to be effective when used on an "as needed" basis. Failing to respond to one antidote after 3 to 4 weeks may require switching

to another, but the change must be tailored to the patient's needs. Periodically discontinuing an effective antidote is recommended every 3 to 6 months to assess whether adaptation to the side effect eventually occurred.

Table 2 lists several pharmacologic antidotes that have been reported to be effective in managing antidepressant sexual side effects, including typical doses reported, type of antidepressant used, which phase of the sexual cycle was reported, and other general safety and tolerance comments. None of these treatments are approved by the U.S. Food and Drug Administration.

Table 2. Pharmacologic Antidotes for Antidepressant-Associated Sexual Dysfunction[a]

Antidote	Dosage	Comments	Reported Effects[b]
Stimulants			
Methylphenidate	5–40 mg/d	For SSRIs or venlafaxine	Libido, arousal, orgasm
Dextroamphetamine	5–40 mg/d	Avoid night dosing (insomnia)	
Pemoline	18.75–75 mg/d	Check liver function	
Ginkgo biloba extract	180–240 mg/d, tid divided doses	Potential increased clotting time, possible flatulence	Libido, arousal, orgasm
Cholinergic enhancers			
Bethanechol	10–50 mg prn	Used for antidepressants with anticholinergic side effect, TCAs, paroxetine	Arousal
Neostigmine	1 hour before sex or 50–200 mg/d, tid divided doses	Cholinergic side effects	
Estrogen creams or lubricants	As needed	For vaginal dryness, atrophy of vaginal tissue	Arousal
Amantadine	100 mg bid	Caution in patients predisposed to psychosis	Orgasm
Cyproheptadine	4–12 mg qhs	MAOIs, TCAs, SSRIs, venlafaxine; watch for reemergence of depressive symptoms; sedating	Orgasm
Buspirone	30–60 mg/d, bid divided doses		Libido, orgasm
Bupropion	75–150 mg/d, qd or bid divided doses	SSRIs or venlafaxine; fluoxetine may raise bupropion levels; usual precautionary measures for bupropion	Libido, arousal, orgasm
Mirtazapine	15–45 mg/d	SSRIs, venlafaxine	Orgasm
Nefazodone	Start 50 mg/d, up to 150 mg/d	SSRIs, venlafaxine	Orgasm
Granisetron	1 mg prn	? Use of other 5-HT_3 antagonists	Orgasm
Sildenafil	50–100 mg/d	Contraindicated with nitrates	Libido, arousal, orgasm
Yohimbine	5.4 mg tid	Can be anxiogenic; ? safety with MAOIs	Libido, arousal, orgasm

[a]Reprinted from Zajecka,[46] with permission. Abbreviations: 5-HT_3 = serotonin-3, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]The sexual phases that the antidote is reportedly effective in treating, out of 3 possible phases that may be affected by the antidepressant.

Buspirone

Buspirone is an anxiolytic that has been shown in case reports to reverse SSRI-induced sexual side effects; it is also among the only antidotes in at least 1 placebo-controlled study[48] to reverse these side effects.[48,49] In the placebo-controlled trial, which assessed the efficacy of buspirone augmentation in patients not responding to monotherapy with an SSRI, 40% of patients (47/117) reported at least 1 type of sexual dysfunction.[48] During 4 weeks of treatment, up to 59% of patients taking buspirone reported improvement in sexual functioning, compared with up to 30% of patients on placebo. The improvement was more pronounced in women and was not related to the antidepressant response. The effect of buspirone compared with placebo on improving sexual function was evident as early as the first week of treatment, and the mean dose was 48.5 mg/day by the end of the 4 weeks.

Several mechanisms may account for the impact of buspirone in the management of SSRI-related sexual side effects. The 5-HT_{1A} effects of buspirone may reduce orgasm delay and diminish SSRI-related hyperprolactinemia.[50,51] Additionally, buspirone may impact sexual side effects via its effect on the dopamine system as well as the α_2 antagonist properties of a major metabolite, 1-pyrimidinylpiperazine, both of which may suppress the SSRI-related effects of serotonin on the dopamine and noradrenergic systems.[52–56] Buspirone may be an ideal treatment in patients taking SSRIs or venlafaxine who have sexual side effects and can also benefit from further antidepressant augmentation.

Bupropion

Bupropion is an antidepressant that appears to be devoid of serotonergic activity and is hypothesized to have norepinephrine- and dopamine-enhancing properties.[57] Several case reports and an open, nonrandomized study[58] suggest buspirone's efficacy in improving SSRI- and venlafaxine-related sexual side effects.[58–61] Ashton and Rosen[58] demonstrated improvement of a variety of SSRI-related sexual side effects and also that further improvement over time may have been correlated with increased doses of up to 225 mg/day, a trend that approached statistical significance for females.[61] Fifteen percent of patients discontinued the bupropion owing to side effects.[61]

The use of bupropion as an antidote requires careful assessment for possible medication interactions, including the usual precautions regarding seizures. Special precautions should be considered when coadministering bupropion with antidepressants that may inhibit both the cytochrome P450 3A4 and cytochrome P450 2D6 hepatic isoenzymes (e.g., fluoxetine, paroxetine), which theoreti-

cally may increase the level of bupropion and one of its major metabolites, hydroxybupropion.[62]

The probable mechanism for the effect of bupropion on improving SSRI-related sexual side effects may be the probable increase of both norepinephrine and dopamine, which may be suppressed by these antidepressants. Similar to buspirone, bupropion may be a reasonable choice in patients taking SSRIs who are experiencing sexual side effects and who have only a partial antidepressant response.

Sildenafil

Sildenafil is a potent phosphodiesterase inhibitor, associated with enhancing nitric oxide effects, resulting in smooth muscle relaxation and increased blood flow to the genital tissues and improving erectile function. Sildenafil is currently approved only for the treatment of erectile dysfunction; however, it has been reported to reverse sexual side effects of several antidepressants in both men and women.[63–71] Sildenafil is among the only pharmacologic antidotes that may be effective on an "as needed" basis, with doses ranging from 50 to 100 mg 30 to 60 minutes prior to sexual activity.

The probable mechanism of sildenafil that improves antidepressant-related sexual side effects includes the obvious increases of penile and possible clitoral/vaginal blood flow. Sildenafil has been reported to improve difficulties associated with arousal, libido, and orgasm delay.[63,71] The effects on libido and orgasm delay may be explained by any indirect benefits increased blood flow may have on achieving, sustaining, and/or improving arousal. Currently, sildenafil is approved only for males with erectile dysfunction, although studies are warranted for the use of this medication in female arousal disorders and in both sexes for antidepressant-related sexual dysfunctions. The usual precautionary measures should be considered when using sildenafil, which include its contraindication with use of nitrates, including the recreational use of amyl nitrate.

Stimulants

Case reports suggest the efficacy of the stimulants methylphenidate, dextroamphetamine, and pemoline to reverse SSRI-related sexual side effects including libido, arousal, and orgasm dysfunctions.[72–75] Some reports suggest intermittent use 1 hour before sexual activity, whereas others report retrospectively that patients improved when the stimulant was added to the treatment as an augmenting agent or for the treatment of SSRI-related asthenia.

Minimal effective doses include 5 mg/day for methylphenidate and dextroamphetamine and 18.75 mg/day for pemoline. Increased doses (e.g., 10 mg twice per day of methylphenidate or dextroamphetamine) may provide greater improvement in some patients; however, higher doses have been reported to have negative impact on sexual function.

Usual precautions should be considered, including abuse potential, avoidance of late-day dosing (to avoid insomnia), cardiovascular effects, and the possibility of increasing sympathetic tone, which may impair erection. Additionally, when using pemoline, routine assessment of liver function and the potential to lower seizure threshold is warranted.

The use of stimulants may be appropriate when patients with sexual side effects require augmentation to enhance an antidepressant or manage symptoms of asthenia, or in patients with comorbid disorders such as attention-deficit/hyperactivity disorder.

Ginkgo Biloba Extract

Ginkgo biloba is an over-the-counter herbal extract that has been shown to increase blood flow. Case reports and 1 uncontrolled study suggest that *Ginkgo biloba* can treat sexual dysfunction associated with SSRIs, including difficulties with libido, arousal, and orgasm.[76] Effective doses ranged from 60 mg/day to 240 mg/day, with a mean dose of 209 mg/day. Recommended dosing of *Ginkgo biloba* as an herbal "supplement" is up to 240 mg/day, in twice- or 3-times-per-day divided doses. Common side effects include gastrointestinal disturbances, flatulence, and headache. *Ginkgo biloba* can alter blood clotting time, which is an important issue for the clinician to consider in patients for whom this may pose potential risk.

The mechanism(s) of *Ginkgo biloba* on reducing antidepressant-related sexual side effects may be secondary to increased peripheral blood flow to the genital organs, possibly similar to the mechanism(s) of sildenafil. Furthermore, preliminary evidence suggests that *Ginkgo biloba* may increase the activity of some neurotransmitters that may offset the negative impact that serotonin may have on sexual function. Both clinicians and patients need to remain cognizant regarding the safety of using over-the-counter herbal compounds, as they may have the potential to cause negative adverse effects as a result of unknown side effects, medication interactions, or other possible complications that remain nebulous because of the lack of regulatory safety procedures that are routine for prescription medications.

Postsynaptic Serotonin Antagonists

Blocking the postsynaptic 5-HT_2 receptor appears to be an important mechanism associated with antidepressants such as nefazodone and mirtazapine, which have minimal, if any, impact on worsening sexual function despite their ability to increase serotonin activity. These antidepressants are reasonable first-line agents for depression, and they have also been shown to improve sexual side effects of SSRIs when used as antidotes.[73,77] The mechanism by which mirtazapine may improve SSRI-related sexual side effects may be further explained by the α_2 antagonist properties, resulting in increased norepinephrine activity, as

well as by possible 5-HT_3 antagonist effects.[73] Granisetron, an antiemetic agent that blocks the 5-HT_3 postsynaptic receptor, was shown in 1 case report to improve SSRI-related orgasm dysfunction in doses of 1 mg as needed.[78]

Further support of the role of 5-HT_2 receptor antagonism comes from a series of case reports[19,79–83] on the use of cyproheptadine to treat sexual side effects associated with TCAs, MAOIs, and SSRIs. Cyproheptadine is an antihistamine that has relatively potent 5-HT_2 antagonistic properties. Doses of cyproheptadine ranged from 4 to 16 mg/day, usually given once per day at bedtime. Side effects associated with cyproheptadine include sedation, increased appetite, and weight gain. Also, reports[79,81] suggest that the use of cyproheptadine may be associated with a return of symptoms (depression and obsessive-compulsive disorder) when used with SSRIs.

Other Pharmacologic Antidotes

Yohimbine, an α_2 antagonist currently approved for the treatment of male erectile dysfunction, has been reported to improve libido, arousal, and orgasm dysfunction associated with TCAs and SSRIs.[11,19,84] The dosing of yohimbine was 5.4 mg 1 to 2 hours before sexual activity or 5.4 mg 3 times per day on a regular basis. The mechanism of yohimbine that improves sexual side effects is most likely secondary to an increase in noradrenergic activity. Common side effects associated with yohimbine include anxiety, agitation, and panic attacks. Therefore, yohimbine should be avoided in patients with a predisposition to panic attacks, anxiety, or residual depressive/anxiety symptoms.

Amantadine is a dopaminergic agent used in the treatment of movement disorders. It has been reported to reverse SSRI-related sexual side effects when used at doses of 100 to 400 mg as needed for at least 2 days before sexual activity or on a regular basis at 100 mg 2 or 3 times per day.[19,85–88] The mechanism of amantadine that reverses SSRI-related sexual side effects is assumed to be secondary to increased dopaminergic effects. Side effects include possible sedation and potential psychosis, and therefore amantadine should be used cautiously in patients with a history of psychotic symptoms.

Other commonly prescribed treatments for antidepressant-related sexual side effects include cholinergic enhancers, such as bethanechol used at 50 to 200 mg/day, given in divided doses 3 times per day, with antidepressants that have significant anticholinergic effects, such as the TCAs.[4] Hormone replacement therapy should be routinely considered in perimenopausal women who have complaints about sexual function or satisfaction; however, the routine risk and benefits of such treatment should always be considered. Vaginal lubricants and estrogen creams should be considered in perimenopausal women, especially women being treated with antidepressants that are associated with significant anticholinergic side effects.

CONCLUSION

Optimal treatment with antidepressants should result in improving all symptoms of the underlying illness, including symptoms associated with sexual function and satisfaction. Conventional antidepressants commonly complicate such outcomes, as they are frequently associated with sexual side effects and therefore make it more difficult to achieve the desired goals of treatment. Sexual complaints at the onset of treatment and throughout treatment require a systematic approach to determine the etiology and tailor appropriate management strategies to the individual patient's needs. A basic understanding of the pathophysiologic mechanism(s) of how certain antidepressants may impact sexual function helps the clinician with using the art and the science of managing these important clinical issues. Choosing an antidepressant with a favorable side effect profile early in the course of treatment may be the most effective strategy for optimal treatment, especially in regard to potential late-onset side effects such as sexual dysfunction.

Drug names: amantadine (Symmetrel and others), bethanechol (Urecholine), bupropion (Wellbutrin), buspirone (BuSpar), cyproheptadine (Periactin), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), granisetron (Kytril), methylphenidate (Ritalin and others), mirtazapine (Remeron), nefazodone (Serzone), neostigmine (Prostigmin and others), nortriptyline (Pamelor and others), paroxetine (Paxil), pemoline (Cylert), sertraline (Zoloft), sildenafil (Viagra), venlafaxine (Effexor), yohimbine (Yocon and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for treating side effects of antidepressants: amantadine, bethanechol, bupropion, buspirone, cyproheptadine, dextroamphetamine, fluoxetine, granisetron, methylphenidate, mirtazapine, nefazodone, neostigmine, nortriptyline, paroxetine, pemoline, sertraline, sildenafil, venlafaxine, yohimbine.

REFERENCES

1. Montejo AL, Llorca G, Izquierdo JA, et al. Antidepressant-induced sexual dysfunction: a multicenter and prospective study using a questionnaire of 693 patients. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 20, 1999; Washington, DC. Abstract NR658:254
2. Segraves RT. Treatment-emergent sexual dysfunction in affective disorder: a review and management strategies. J Clin Psychiatry Monograph 1993; 11(1):57–60
3. Harvey KV, Balon R. Clinical implications of antidepressant drug effects on sexual dysfunction. Ann Clin Psychiatry 1995;7:189–201
4. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. J Clin Psychiatry 1994; 55:406–413
5. Segraves RT. Antidepressant-induced sexual dysfunction. J Clin Psychiatry 1998;59(suppl 4):48–54
6. Balon R, Yeragani VK, Pohl R, et al. Sexual dysfunction during antidepressant treatment. J Clin Psychiatry 1993;54:209–212
7. Lane RM. A critical review of selective serotonin reuptake inhibitor–related sexual dysfunction; incidence, possible aetiology and implications for management. J Psychopharmacol 1997;11:72–82
8. Baier D, Philipp M. Effects of antidepressants on sexual function. Fortschr Neurol Psychiatr 1994;62:14–21
9. Herman JB, Brotman AW, Pollack MH, et al. Fluoxetine-induced sexual

dysfunction. J Clin Psychiatry 1990;51:25–27
10. Zajecka J, Fawcett J, Schaff M, et al. The role of serotonin in sexual dysfunction: fluoxetine-associated orgasm dysfunction. J Clin Psychiatry 1991;52:66–68
11. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 1992;53:119–122
12. Harrison WM, Rabkin JG, Ehrhardt AA, et al. Effects of antidepressant medication on sexual function: a controlled study. J Clin Psychopharmacol 1986;6:144–149
13. Monteiro WO, Noshirvani HF, Marks IM, et al. Anorgasmia from clomipramine in obsessive-compulsive disorder: a controlled trial. Br J Psychiatry 1987;151:107–112
14. Bisserbe JC, Lane RM, Flament M, et al. A double-blind parallel comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. Eur Psychiatry 1997;12:82–93
15. Lepine JP, Wiseman R. Treatment of severe major depression: a double-blind study of sertraline and clomipramine. Eur Neuropsychopharmacol 1996;6:123
16. Pigott TA, Pato MT, Bernstein SE, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 1990;47:926–932
17. Freeman PL, Trimble MR, Deakin JF, et al. Fluvoxamine versus clomipramine in the treatment of obsessive-compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. J Clin Psychiatry 1994; 55:301–305
18. Smeraldi E, Erzegovesi S, Bianchi I. Fluvoxamine vs clomipramine treatment in obsessive-compulsive disorder: a preliminary study. N Trends Exp Clin Psychiatry 1992;8:63–65
19. Ashton AK, Hamer R, Rosen RC. Serotonin reuptake inhibitor-induced sexual dysfunction and its treatment: a large-scale retrospective study of 596 psychiatric outpatients. J Sex Marital Ther 1997;23:165–175
20. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57 (suppl 2):53–62
21. Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: a review. J Clin Psychiatry 2001;62(suppl 3):22–34
22. Zajecka J, Dunner DL, Hirschfeld RMA, et al. Sexual function and satisfaction in the treatment of chronic depression with nefazodone, psychotherapy, and their combination. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 16, 2000; Chicago, Ill. Abstract NR443:176
23. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997;58:532–537
24. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993;54:459–465
25. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. Arch Gen Psychiatry 1989;46:275–284
26. Bitran D, Hull EM. Pharmacological analysis of male rat sexual behavior. Neurosci Biobehav Rev 1988;11:365–389
27. Sullivan G, Lukoff D. Sexual side effects of antipsychotic medication: evaluation and interventions. Hosp Community Psychiatry 1990;41: 1238–1241
28. Baldessarini RJ, Marsh E. Fluoxetine and side effects. Arch Gen Psychiatry 1990;47:191–192
29. Meltzer HY, Young M, Metz J, et al. Extrapyramidal side effects and increased serum prolactin following fluoxetine, a new antidepressant. J Neural Transm 1979;45:165–175
30. Bouchard RH, Pourcher E, Vincent P. Fluoxetine and extrapyramidal side effects. Am J Psychiatry 1989;146;1352–1353
31. Cohen MA, Davies PH. Drug therapy and hyperprolactinemia. Adverse Drug React Bull 1998;190:723–726
32. Cowen PJ, Sargent PA. Changes in plasma prolactin during SSRI treatment: evidence for a delayed increase in 5-HT neurotransmission. J Psychopharmacol 1997;4:345–348
33. Amsterdam JD, Garcia-Espana F, Goodman D, et al. Breast enlargement during chronic antidepressant therapy. J Affect Disord 1998;46:151–156
34. Bronzo MR, Stahl SM. Galactorrhea induced by sertraline [letter]. Am J Psychiatry 1993;150:1269–1270
35. Hall MJ. Breast tenderness and enlargement induced by sertraline [letter]. Am J Psychiatry 1994;129:738
36. Pollack MH, Reiter S, Hammerness P. Genitourinary and sexual adverse effects of psychotropic medication. Int J Psychiatry Med 1992;22:305–327
37. Finkel MS, Laghrissi-Thode F, Pollock BG, et al. Paroxetine is a novel nitric oxide synthetase inhibitor. Psychopharmacol Bull 1996;32:653–658
38. Stahl SM. How psychiatrists can build new therapies for impotence [BRAINSTORMS]. J Clin Psychiatry 1998;59:47–48
39. Crenshaw TL, Goldberg JP, eds. Sexual Pharmacology: Drugs That Affect Sexual Functioning. New York, NY: WW Norton & Co; 1996:369–408
40. Jacobsen FM. SSRI-induced sexual dysfunction. Am Soc Clin Psychopharmacol Progress Notes 1994(a);5:1–4
41. Stahl SM. Psychopharmacology of Antidepressants. London, England: Martin Dunitz Ltd; 1998:55–56
42. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther 1997;23:176–194
43. Benazzi F, Mazzoli M. Fluoxetine-induced sexual dysfunction: a dose-dependent effect? Pharmacopsychiatry 1994;27:246
44. Zajecka J, Mitchell S, Fawcett J. Treatment-emergent changes in sexual function with selective serotonin reuptake inhibitors as measured with the Rush Sexual Inventory. Psychopharmacol Bull 1997;33:755–760
45. Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review. J Clin Psychiatry 1997;58:291–297
46. Zajecka JM. Clinical issues in long-term treatment with antidepressants. J Clin Psychiatry 2000;61(suppl 2):20–25
47. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. Am J Psychiatry 1995;152:1514–1516
48. Landen MSG, Eriksson E, Agren H, et al. Buspirone provides relief for sexual side effects induced by SSRIs. In: New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association; June 4, 1998; Toronto, Ontario, Canada. Abstract NR694:255
49. Norden MJ. Buspirone treatment of sexual dysfunction associated with selective serotonin re-uptake inhibitors. Depression 1994;2:109–112
50. Ahlenius S, Larsson K, Svensson L, et al. Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. Pharmacol Biochem Behav 1981;15:758–792
51. Tome MB, Isaac M. Effects of augmenting agents on prolactin and cortisol in resistant depression [poster]. Presented at the 36th annual meeting of the American College of Neuropsychopharmacology; Dec 8–12, 1997; Waikoloa, Hawaii
52. Gelenberg AJ, Bassuk EL, Schoonover SC. The Practitioner's Guide to Psychoactive Drugs. 3rd ed. New York, NY: Plenum; 1991:1997
53. Jacobsen FM. Possible augmentation of antidepressant response by buspirone. J Clin Psychiatry 1991;52:217–220
54. Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. J Clin Psychiatry 1993;54: 269–271
55. Fahlen T, Agren H, Edstom A, et al. Buspirone augmentation of SSRI therapy in treatment refractory depression [abstract]. Eur Neuropsychopharmacol 1996;6(suppl 3):127
56. Menkes DB. Buspirone augmentation of sertraline. Br J Psychiatry 1995; 166:823–824
57. Ascher JA, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395–401
58. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor–induced sexual dysfunction. J Clin Psychiatry 1998;59:112–115
59. Labbate LA, Pollack MH. Treatment of fluoxetine-induced sexual dysfunction with bupropion: a case report. Ann Clin Psychiatry 1994;6:13–15
60. Grimes JB, Labbate LA. Spontaneous orgasm with the combined use of bupropion and sertraline. Biol Psychiatry 1996;40:1184–1185
61. Bodkin JA, Lasser RA, Wines JD Jr, et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry 1997;58:137–145
62. Pollock BG, Sweet RA, Kirshner M, et al. Bupropion plasma levels and CYP2D6 phenotype. Ther Drug Monit 1996;18:581–585
63. Fava M, Rankin MA, Alpert JE, et al. An open trial of oral sildenafil in antidepressant-induced sexual dysfunction. Psychother Psychosom 1998; 67:328–331
64. Nurnberg HG, Hensley PL, Lauriello J, et al. Sildenafil for women patients with antidepressant-induced sexual dysfunction. Psychiatr Serv 1999;50: 1076–1078
65. Nurnberg HG, Lauriello J, Hensley PL, et al. Sildenafil for sexual dysfunc-

tion in women taking antidepressants [letter]. Am J Psychiatry 1999;156: 1664
66. Ashton AK. Sildenafil treatment of paroxetine-induced anorgasmia in a woman [letter]. Am J Psychiatry 1999;156:800
67. Ashton AK, Bennett RG. Sildenafil treatment of serotonin reuptake inhibitor-induced sexual dysfunction [letter]. J Clin Psychiatry 1999;60:194–195
68. Schaller JL, Behar D. Sildenafil citrate for SSRI-induced sexual side effects. Am J Psychiatry 1999;156:156–157
69. Gupta S, Masand P, Ashton AK, et al. Phenelzine-induced sexual dysfunction treated with sildenafil. J Sex Marital Ther 1999;25:131–135
70. Balon R. Fluvoxamine-induced erectile dysfunction responding to sildenafil. J Sex Marital Ther 1998;24:313–317
71. Rosenberg KP. Sildenafil citrate for SSRI-induced sexual side effects [letter]. Am J Psychiatry 1999;156:157
72. Bartlik BD, Kaplan P, Kaplan HS. Psychostimulants apparently reverse sexual dysfunction secondary to selective serotonin re-uptake inhibitors. J Sex Marital Ther 1995;21:264–271
73. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997;340:249–258
74. Gitlin MJ. Treatment of sexual side effects with dopaminergic agents [letter]. J Clin Psychiatry 1995;56:124
75. Roeloffs C, Bartlik B, Kaplan PM, et al. Methylphenidate and SSRI-induced sexual side effects [letter with reply]. J Clin Psychiatry 1996; 57:548
76. Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. J Sex Marital Ther 1998;24:139–143
77. Reynolds RD. Sertraline-induced anorgasmia treated with intermittent nefazodone [letter]. J Clin Psychiatry 1997;58:89
78. Nelson EB, Keck PE Jr, McElroy SL. Resolution of fluoxetine-induced sexual dysfunction with the 5-HT_3 antagonist granisetron [letter]. J Clin Psychiatry 1997;58:496–497
79. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. J Clin Psychiatry 1991;52:163–164
80. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. J Clin Psychiatry 1991; 52:261–262
81. McCormick S, Olin J, Brotman AW. Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. J Clin Psychiatry 1990;51: 383–384
82. Aizenberg D, Zemishlany Z, Weizman A. Cyproheptadine treatment of sexual dysfunction induced by serotonin reuptake inhibitors. Clin Neuropharmacol 1995;18:320–324
83. Lauerma H. Successful treatment of citalopram-induced anorgasmia by cyproheptadine. Acta Psychiatr Scand 1996;93:69–70
84. Hollander E, McCarley A. Yohimbine treatment of sexual side effects induced by serotonin reuptake blockers. J Clin Psychiatry 1992;53:207–209
85. Balogh S, Hendricks SE, Kang J. Treatment of fluoxetine-induced anorgasmia with amantadine [letter]. J Clin Psychiatry 1992;53:212–213
86. Shrivastava RK, Shrivastava S, Overweg N, et al. Amantadine in the treatment of sexual dysfunction associated with selective serotonin reuptake inhibitors. J Clin Psychopharmacol 1995;15:83–84
87. Balon R. Intermittent amantadine for fluoxetine-induced anorgasmia. J Sex Marital Ther 1996;22:290–292
88. Massand PS, Reddy N, Gregory R. SSRI-induced sexual dysfunction successfully treated with amantadine. Depression 1995;2:319–321